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(21) International Application Number: PCT/JP93/01543 (22) International Filing Date: 26 October 1993 (26.10.93) (30) Priority data: 4/310772 27 October 1992 (27.10.92) JP (71) Applicants (for all designated States except US): NIPPON KAYAKU KABUSHIKI KAISHA [JP/JP]; 11-2, Fujimi 1-chome, Chiyoda-ku, Tokyo 102 (JP). ORION-YHTY-MA OY [FI/FI]; P.O. Box 65, FIN-02101 Espoo (FI). (72) Inventors; and (75) Inventors/Applicants (for US only) : ITO, Junpei [JP/JP]; 1090, Kamiochiai, Yono-shi, Saitama 338 (JP). MIYAZAKI, Osamu [JP/JP]; 24-21, Kitazonocho, Kawaguchi-shi, Saitama 333 (JP). EKIMOTO, Hisao [JP/JP]; Takku Puraza 803, 2-11-1, Shimo, Kita-ku, Tokyo 115 (JP). KOYAMA, Michinori [JP/JP]; 2-24-6, Towa, Adachi-ku, Tokyo 120 (JP). SAINO, Tetsushi [JP/JP]; 5-11-14-101, Hachioji, Yono-shi, Saitama 338 (JP). KANGAS, Lauri [FI/FI]; WARRI, Anni [FI/FI]; Orion-yhtyma Oy, P.O. Box 65, FIN-02101 Espoo (FI).		(74) Agents: ASAMURA, Kiyoshi et al.; Room 331, New Ohtemachi Building, 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo 100 (JP). (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: USE OF NON STEROIDAL ANTI ESTROGENS FOR AUTOIMMUNE DISEASES			
(57) Abstract Disclosed is use of nonsteroidal anti-estrogen compounds such as toremifene citrate as active ingredient for treating autoimmune diseases.			

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<p>(54) Title: USE OF NON STEROIDAL ANTI ESTROGENS FOR AUTOIMMUNE DISEASES (57) Abstract Disclosed is use of nonsteroidal anti-estrogen compounds such as toremifene citrate as active ingredient for treating autoimmune diseases.</p>		

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DESCRIPTION

USE OF NON-STEROIDAL ANTIESTROGENS FOR AUTOIMMUNE DISEASES

1 [Technical Field]

The present invention relates to use of nonsteroidal anti-estrogen compounds (hereinafter referred to as nonsteroidal anti-estrogens) such as toremifene, expected as a remedy for autoimmune diseases.

The autoimmune diseases include collagen diseases and the like. In light of affected parts by the diseases, there are mentioned, for example, degenerative diseases of supporting tissues and connective tissues; autoimmune degenerative diseases of salivary glands, particularly Sjögren's disease; autoimmune degenerative diseases of kidneys, particularly systemic lupus erythematoses and glomerulonephritis; autoimmune degenerative diseases of joints, particularly rheumatoid arthritis; and autoimmune degenerative diseases of blood vessels such as generalized necrotizing angitis and granulomatous angitis; and multiple sclerosis.

20 [Background Art]

Immunosuppressants, nucleic acid antagonists, antimetabolites, etc., are used in the medicinal treatment of autoimmune diseases today. Anti-inflammatory agents, anticoagulants, etc., are also used in the

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1 symptomatic therapies of the diseases. The effects of
these agents are, however, not yet sufficient.

It is known that the immunosuppressants have
side effects of provoking diabetes, renal disorders,
5 infectious diseases, etc. Also the use of the nucleic
acid antagonist or antimetabolite is frequently
accompanied by side effects such as hepatic disorders
and medullary disorders. Thus the medicinal treatment
of autoimmune diseases is so far very insufficient.

10 It has been demanded to develop a remedy for
autoimmune diseases which acts on the immune system and
which has a function mechanism different from that of
conventional drugs for the diseases and less serious
side effects.

15 [Disclosure of Invention]

After intensive investigations made for the
purpose of finding the above-described remedy, the
present inventors have found that nonsteroidal anti-
estrogens have an excellent therapeutic effect on the
20 autoimmune diseases and thus, based on this finding,
completed the present invention.

The present invention relates to a remedy for
autoimmune diseases which comprises as active ingredient
a nonsteroidal anti-estrogen or a pharmaceutically
25 acceptable salt thereof.

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1 [Brief Description of Drawings]

Fig. 1 shows survival times of animals (NZBxNZW F1 mice:B/W F1 mice) which accepted different doses of toremifene.

5 [Best Mode for Carrying Out the Invention]

The nonsteroidal anti-estrogen compounds usable in the present invention are those having a triphenyl C₂ - C₅ alkene or triphenyl C₂ - C₅ alkane skeleton. Preferably, they are C₂ - C₅ alkenes or C₂ - C₅ alkanes having three phenyl substituents at the 1-
10 position and 2-position, wherein any of the phenyl groups may have a substituent such as a mono- or di-lower alkyl (C₁ - C₃) amino lower alkoxy (C₁ - C₃) group, or a hydroxyl group, or the alkyl group in the above
15 alkenes or alkanes may have a substituent such as a halogen.

Examples of these compounds include toremifene (JP-B-4 19973), tamoxifen (JP-B-59 21861), 4-hydroxy-tamoxifen (JP-A-54 44644), 3-hydroxytamoxifen (JP-A-57
20 122049) and N-demethyltoremifene or 4-hydroxytoremifene (JP-A-3 163015). Toremifene is particularly preferred. It is well-known that these compounds have an anti-neoplastic effect (see Cancer Chemotherapy and Pharmacology, 17, 109-113 (1986) and the above-mentioned
25 patent publications).

The pharmaceutically acceptable salts thereof include, for example, hydrochlorides, sulfates,

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1 citrates, tartrates and phosphates.

Drugs usable in combination with the nonsteroidal anti-estrogens in the medicinal treatment of autoimmune diseases include glucocorticoids (e.g. 5 prednisolone, prednisone, cortisol).. Prednisolone is preferred.

The glucocorticoids themselves have an effect of treating the autoimmune diseases. The nonsteroidal anti-estrogens or a pharmaceutically acceptable salt 10 thereof according to the present invention concomitant with the glucocorticoids synergistically improve the effect of treating.

The remedy of the present invention particularly exhibits an excellent remedial effect on 15 systemic lupus erythematoses.

Therefore the present invention relates to the following:

- (i) a remedy for autoimmune diseases which comprises as active ingredient a nonsteroidal anti- 20 estrogen or a pharmaceutically acceptable salt thereof;
- (ii) a remedy recited in (i), wherein the nonsteroidal anti-estrogen is a compound having a triphenyl C₂-C₅ alkene or triphenyl C₂-C₅ alkane skeleton;
- (iii) a remedy recited in (i) or (ii), wherein the 25 active ingredient is toremifene or a pharmaceutically acceptable salt thereof;
- (iv) a remedy recited in (i) or (ii), wherein the autoimmune diseases are collagen diseases, autoimmune

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- 1 degenerative diseases of kidneys such as nephritis,
particularly glomerulonephritis, and autoimmune
degenerative diseases of blood vessels, salivary glands
and joints;
- 5 (v) a remedy recited in (i) or (ii), wherein the
autoimmune diseases are systemic lupus erythematoses;
and
(vi) a remedy recited in (i) or (ii) for
concomitant use with a glucocorticoid.
- 10 The pharmaceutical composition of the present
invention is administered orally, parenterally or
intravenously.

Usually, a pharmaceutically effective amount
of the active ingredient is used in combination with a
15 suitable medicinal carrier or other auxiliaries. The
term "pharmaceutically effective amount" herein means an
amount capable of exhibiting the intended pharmacolog-
ical activity without causing unfavorable side effects.
The accurate amount varies in each case depending on
20 various factors such as administration methods,
individual natures of the patients and situations in
which the patient accepts the remedy and, as a matter of
course, structures of derivatives to be administered.

Dose of the active ingredient for adult is
25 usually 10 to 1000 mg/day, preferably 20 to 500 mg/day,
more preferably 30 to 300 mg/day.

In the case of the concomitant use, dose of
the glucocorticoid for adult is 1 to 100 mg/day,

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1 preferably 2 to 60 mg, and that of the nonsteroidal
anti-estrogen or the pharmaceutically acceptable salt
thereof for adult is 10 to 700 mg/day, preferably 20 to
500 mg/day, more preferably 30 to 300 mg/day.

5 The medicinal carrier or other auxiliaries
generally usable in combination with the active
ingredient according to the present invention may be any
of solid and liquid ones and usually selected in
consideration of an administration route. Examples of
10 the solid carrier include lactose, sucrose, gelatin and
agar, and those of the liquid carrier include water,
syrup, peanut oil and olive oil. Other suitable
carriers and auxiliaries known by those skilled in the
art are also usable. The active ingredient according to
15 the present invention can be combined with the carrier
or other auxiliaries to form any of various acceptable
preparations such as tablets, capsules, suppositories,
liquid, emulsion and powder.

In the preparations of the remedy of the
20 present invention, the amount of the nonsteroidal anti-
estrogen or the pharmaceutically acceptable salt thereof
can widely vary depending on the preparation, etc.
Usually, the amount is 0.01 ~ 100% by weight, preferably
0.1 ~ 70% by weight, and the balance contains the
25 medicinal carrier or other auxiliaries.

MRL/Mp-lpr/lpr mice spontaneously develop a
lethal glomerulonephritis, angitis, sialadenitis,
polyarthrititis, etc., concurrently with the deposition of

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1 an immune complex with age. Therefore, they are widely
used as experimental models for human systemic lupus
erythematoses, Sjögren's disease, rheumatoid arthritis
and autoimmune angitis such as multiple arteritis.

5 The present invention will be explained
referring to examples on suppression of lymphadenopathy
glomerulonephritis, angitis, sialadenitis and arthritis
of MRL/Mp-lpr/lpr mice with the nonsteroidal anti-
estrogen compound according to the present invention.

10 The nonsteroidal anti-estrogen such as
toremifene and the pharmaceutically acceptable salt
thereof according to the present invention exhibit an
excellent remedial effect on degenerative diseases such
as autoimmune diseases, for example, systemic lupus
15 erythematoses.

Example 1

Treatment of spontaneous autoimmune diseases of MRL/Mp-
lpr/lpr mice by administration of 2[4-(Z)-4-chloro-1,2-
diphenyl-1-butenyl]phenoxy-N,N-dimethylethylamine
20 citrate (toremifene citrate)

Eight-week old female MRL/Mp-lpr/lpr mice
(Clea Japan, Inc.) were used in this examination.
Toremifene citrate (JP-B-4 19973) was suspended in
carboxymethylcellulose to prepare a 0.5% suspension.
25 This compound (100 mg/kg) was orally administered to
each mouse once a day for 13 weeks.

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1 (A) Inhibition of swelling of spleen and lymph
node of MRL/Mp-lpr/lpr mice with toremifene citrate

Repeated oral administration of 100 mg/kg of
toremifene citrate once a day for 13 weeks inhibited the
5 swelling of the spleen and lymph node of each mouse (see
Table 1).

The spleen and lymph nodes of the MRL/Mp-
lpr/lpr mice are seriously swollen with age due to the
presence of the lymphoproliferation gene (lpr). The lpr
10 codes for the Fas antigen in each mouse. However, in
the MRL/Mp-lpr/lpr mice, an abnormality of the genes
disturbs the expression of the Fas antigen. As a
result, autoreactive T-cells are not subjected to
negative selection through the Fas antigen in the thymus
15 and appear in the peripheral tissues to cause the
swelling of the lymphoid organs and autoimmune symptoms.
The presence of the autoreactive T-cells was confirmed
also in the autoimmune diseases of human beings, such as
rheumatoid arthritis.

20 The results of this study indicated that the
nonsteroidal anti-estrogen compounds such as toremifene
citrate are capable of inhibiting the appearance of the
autoreactive T-cells, thereby suppressing the swelling
of spleen and lymph node to treat the autoimmune
25 diseases.

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Table 1: Effect of toremifene citrate¹⁾ on swelling
of spleen and lymph node MRL/Mp-lpr/lpr
mice

Group	Number of animals	$\frac{\text{Spleen weight } ^{4)}}{\text{Body weight}}$	$\frac{\text{Lymph node } ^{5)}\text{ weight}}{\text{Body weight}}$
Control ²⁾	11	2.34 ± 0.74 ³⁾	6.77 ± 1.70
Toremifene citrate treatment	12	1.38 ± 1.06	3.11 ± 1.43

1) Toremifene citrate (100 mg/kg) was orally
administered to 8-week old mice once a day for 13 weeks.

2) Only 0.5% carboxymethylcellulose was given to the
mice of the control group.

3) Standard deviation

4) $\text{Spleen weight/body weight} = \frac{\text{Weight of spleen}}{\text{Body weight of mouse}} \times 100$

5) $\text{Lymph node weight/body weight} = \frac{\text{Weight of lymph node}}{\text{Body weight of mouse}} \times 100$

(B) Suppression of renal disorder of MRL/Mp-
lpr/lpr mouse with toremifene citrate

10 An autopsy was performed on the mice of the
control group and the toremifene citrate treated group
after the completion of the administration to examine
their kidneys pathohistologically. The blood urea
nitrogen (BUN) of the serum in each group was examined
15 to confirm changes in the renal function. As shown in

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1 Table 2, toremifene citrate ameliorated the
glomerulonephritis and healed the renal function in the
MRL/Mp-lpr/lpr mice.

The glomerulonephritis of the MRL/Mp-lpr/lpr
5 mice is caused by the deposition of immunocomplexes.
Also in the case of the autoimmune diseases such as
systemic lupus erythematoses (SLE) of human, the
patients suffer from glomerulonephritis concurrent with
the deposition of the immunocomplex. The results
10 indicated that the nonsteroidal anti-estrogen compounds
such as toremifene citrate are effective remedies for
the degenerative diseases of the kidney, such as the SLE
with renal syndrome and glomerulonephritis.

Table 2: Improvement of renal function and amelioration
of glomerulonephritis of MRL/Mp-lpr/lpr mice
with toremifene citrate

Group	Number of animals	Glomerulonephritis ¹⁾	BUN (mg/dl) ²⁾
Control	11	2.4 ± 0.7 ³⁾	43.1±23.9
Toremifene citrate treatment	12	1.2 ± 0.7	24.6±4.9

1) The kidney was fixed in 10% buffered formalin, and
15 then paraffin sections thereof were prepared by an
ordinary method to prepare HE and PAS stained
specimens. The extent of the disorder of the renal

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1 glomeruli was scored and classified into the
following groups:

- 0 (no disorder),
- 1 (slight disorder),
- 5 2 (medium disorder), and
- 3 (heavy disorder).

Twenty-five renal glomeruli were observed for each mouse and the average thereof was calculated.

- 2) The BUN was determined with a Fuji Dry Chem
10 Analyzer.
- 3) Standard deviation.

(C) Inhibition by toremifene citrate of
sialadenitis, angitis and arthritis of MRL/Mp-lpr/lpr
mice

15 The salivary gland, renal blood vessel and knee
joint of each mouse in the control group and the
toremifene citrate treated group were histopathological-
ly examined.

As shown in Table 3, toremifene citrate
20 prevented the mice from being attacked by sialadenitis,
angitis and arthritis.

These results indicated that the nonsteroidal
anti-estrogen compounds such as toremifene citrate and
tamoxifen citrate can be used as the remedy for
25 autoimmune sialadenitis (Sjögren's disease), autoimmune
arthritis (chronic articular rheumatism) and autoimmune
angitis (necrotizing angitis and granulomatous angitis).

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Table 3: Effect of toremifene citrate for preventing MRL/Mp-lpr/lpr mice from being attacked by sialadenitis, angitis and arthritis

Group	Number of animals	Sialadenitis 1)	Angitis 1)	Arthritis 1)
Control	11	2.2±0.6 ²⁾	2.1±0.7	1.6±0.9
Toremifene citrate treatment	12	0.9±0.8	0.9±0.8	0.4±0.5

- 1) The salivary gland, kidney and knee joint were fixed in 10% buffered formalin, and then paraffin sections thereof were prepared by an ordinary method to prepare HE and PAS stained specimens. The extent of the disorder was scored and classified into the following groups:

- 0 (no disorder),
- 1 (slight disorder),
- 2 (medium disorder), and
- 3 (heavy disorder).

- 2) Standard deviation.

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1 Example 2

Effect of concomitant use of toremifene citrate with
glucocorticoid on MRL/Mp-lpr/lpr mice

Twelve-week old female MRL/Mp-lpr/lpr mice were
5 used in the examination. Thirty milligrams per kg or 15
mg/kg of toremifene citrate (TOR) was orally
administered to each mouse twice a day for 9 weeks from
the 12th week to the 21st week. A glucocorticoid
(prednisolone), 8, 4 and 2 mg/kg/day, were subcutaneous-
10 ly administered to mice once a day as a positive control
drug. The concomitant use of tremifene with the
glucocorticoid was also carried out according to the
same regimen as above. The kidney was taken out from
each mouse the day after the completion of the whole
15 administration period and fixed in a PLP fixative.
Frozen sections were made from the fixed kidney and used
for an immunostaining with an anti-Mac-2 monoclonal
antibody (Hybritec Inc., San Diego, USA). The number of
Mac-2 positive cells (activated macrophages) invading
20 each of 10 to 20 glomeruli of the kidney, which is
hereinafter referred to as Mac 2 number, was counted
under a microscopy to determine an average Mac 2 number
per glomerulus. The degree of severeness of
glomerulonephritis was estimated in terms of the average
25 Mac 2 number (n = 13 for each group). Table 4 shows the
results.

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Table 4: Suppression of glomerulonephritis of MRL/Mp-lpr/lpr mice by concomitant use of toremifene citrate with glucocorticoid

Group		Mac 2 number
Control		7.5 ± 1.5
Toremifene citrate (TOR)	30 mg/kg	6.2 ± 1.0
	15 mg/kg	6.5 ± 1.2
Prednisolone (P)	8 mg/kg	5.8 ± 0.8
	4 mg/kg	7.9 ± 0.7
	2 mg/kg	9.4 ± 1.0
Control		11.3 ± 1.2
Prednisolone (P)	4 mg/kg	9.1 ± 1.4
	2 mg/kg	7.7 ± 1.0
P 4 mg/kg & TOR 30 mg/kg (concomitant use)		4.1 ± 0.5*
P 4 mg/kg & TOR 15 mg/kg (concomitant use)		4.3 ± 0.5*
P 4 mg/kg & TOR 7.5 mg/kg (concomitant use)		3.5 ± 0.5*
P 2 mg/kg & TOR 30 mg/kg (concomitant use)		3.6 ± 0.7*
P 2 mg/kg & TOR 15 mg/kg (concomitant use)		2.8 ± 0.5*
P 2 mg/kg & TOR 7.5 mg/kg (concomitant use)		4.3 ± 0.6*

* P < 0.01 (t-test)

1 All the groups treated by concomitant use of toremifene citrate (TOR) with prednisolone (P) exhibited significant decrease in Mac 2 number as compared with the control and the prednisolone treated group. On the

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- 1 other hand, the prednisolone treated group and the
toremifene citrate treated group did not exhibit any
significant decrease in Mac 2 number as compared with
the control. The results of these tests indicates that
5 the concomitant use of the both drugs synergistically
suppresses the glomerulonephritis.

Example 3

Comparison of survival time

- NZB x NZW mice (B/W F1 mice) were used as a
10 pathological model of autoimmune diseases (systemic
lupus erythematoses). Effect of toremifene citrate on
the survival time of the animals was investigated.

Experimental animals:

- F1-hybrids of NZB (female) and NZW (male) mice (B/W F1
15 mice): Imported from Bomholtgaard, Denmark at the age of
five weeks.

Test groups and doses:

- Control (male): administration polyethyleneglycol (peg)
3 times a week per os
20 Control (female): administration peg 3 times a week per
os
Toremifene citrate 30 mg/kg/day: administration 70
mg/kg in polyethylene glycol solution
3 times a week per os to female
25 NZB x NZW F1 mice
Toremifene citrate 3 mg/kg/day: administration 7 mg/kg
in polyethylene glycol solution 3 times

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1 a week per os to female NZB x NZW F1
mice

The survival time of the animals in different
test groups is presented in Fig. 1. All but two female
5 control animals have died during the 'almost two years'
follow-up time. Fifty percents of the animals in this
group died before/at the age of 40 weeks, and 20% (4/20)
were alive after one year.

In the male control group, five animals died
10 during the first 24 weeks (not shown in Fig. 1) due to
aggressive behaviour and thereby acquired infection.
These five were excluded from the results. Forty-seven
percents of the male control mice are still alive after
almost two years' time.

15 In both toremifene treatment groups the life
span of the animals has lengthened clearly when compared
to the female control animals. In the 3 mg/kg
toremifene treatment group only one (1/20) animal had
died at/before the age of 40 weeks and three (3/20)
20 animals in the 30 mg/kg toremifene group.

After one year 80% and 85% of the animals were
alive in the 3 mg/kg and 30 mg/kg toremifene treated
groups, respectively, which is nearer the percentage of
the male control animals ($\approx 90\%$) than that of the female
25 control group (20%).

Moreover, 25% (5/20) and 10% (2/20) of the
animals are still alive after 'almost two years' time in
the lower and higher toremifene dosage group, respec-

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1 tively.

The follow-up data of 60 female and 15 male F1-
hybrids of NZB x NZW F1 mice (B/W F1 mice) show that
toremifene treatment has clearly extended the life span
5 of female mice.

Example 4

Examples of preparations comprising the
nonsteroidal anti-estrogen or the pharmacologically
acceptable salt thereof as active ingredient will be
10 given below, which by no means limit the preparations of
the present invention.

Preparation Example 1

Formulation of prepared 200 mg tablet.

	Toremifene citrate	20 mg
15	Starch	85 mg
	Lactose	90 mg
	Magnesium stearate	5 mg

Preparation Example 2

Formulation of prepared 200 mg tablet.

20	Tamoxifen citrate	20 mg
	Starch	85 mg
	Lactose	90 mg
	Magnesium stearate	5 mg

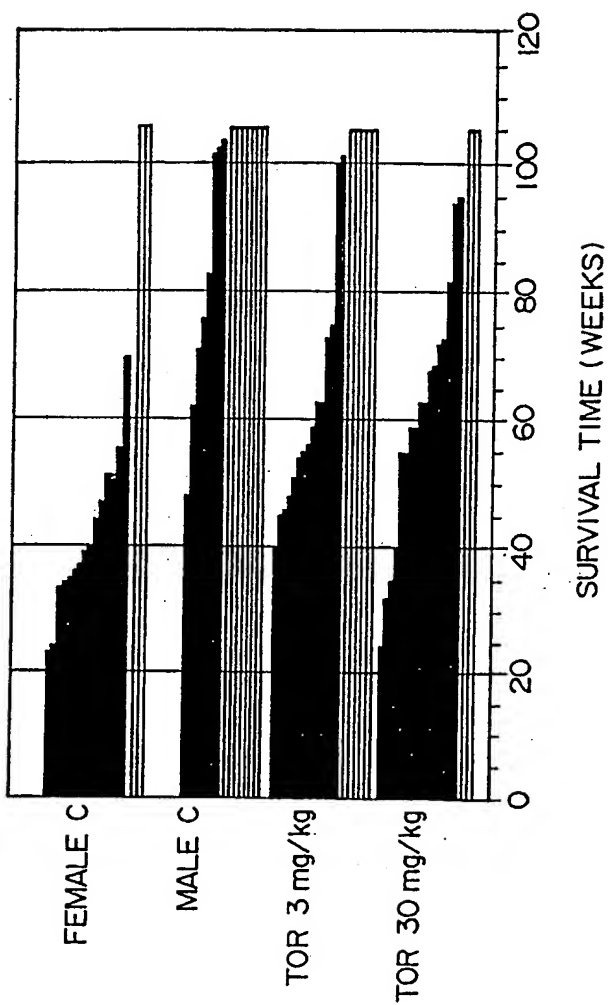
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CLAIMS

1. A remedy for autoimmune diseases which comprises as active ingredient a nonsteroidal anti-estrogen or a pharmaceutically acceptable salt thereof.
2. A remedy according to claim 1, wherein said nonsteroidal anti-estrogen is a compound having a triphenyl C₂-C₅ alkene or triphenyl C₂-C₅ alkane skeleton.
3. A remedy according to claim 1, wherein said nonsteroidal anti-estrogen compound is toremifene.
4. A remedy according to claim 1, wherein said autoimmune diseases are autoimmune degenerative diseases of kidneys.
5. A remedy according to claim 1, wherein said autoimmune diseases are autoimmune degenerative diseases of salivary glands.
6. A remedy according to claim 1, wherein said autoimmune diseases are autoimmune degenerative diseases of blood vessels.
7. A remedy according to claim 1, wherein said autoimmune diseases are systemic lupus erythematoses.
8. A remedy according to claim 1, wherein said autoimmune diseases are glomerulonephritis.
9. A remedy according to claim 1, wherein said nonsteroidal anti-estrogen compound is toremifene and said autoimmune diseases are autoimmune degenerative diseases of joints.
10. A remedy according to claim 1 for concomitant use with a glucocorticoid.

1 / 1

FIG. 1



INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/00 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BR. J. DERMATOL. vol. 121, no. 1, 1989 pages 135 - 137 C.J.M. STEPHENS ET AL 'Autoimmune progesterone dermatitis responding to tamoxifen.' see the whole document ---	1,2
X	ANN. DERMATOL. VENEREOL. vol. 188, no. 8, 1991 pages 551 - 555 F. FREYCHET ET AL. 'La dermatose auto-immune a la progestérone.' see the whole document --- -/-	1,2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

21 December 1993

Date of mailing of the international search report.

04.01.94

Name and mailing address of the ISA

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Authorized officer

Klaver, T

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 93/01543

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. CLIN. LAB. IMMUNOL. vol. 13, no. 1, 1984 pages 11 - 14 A. D. STURGESS ET AL 'Effects of the estrogen antagonist tamoxifen on disease indices in systemic lupus erythematosus.'	
A	EP,A,0 415 623 (A.L. HARRIS ET AL) 6 March 1991 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 93/01543

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0415623	06-03-91	US-A- 4990538	05-02-91
		AU-B- 633954	11-02-93
		AU-A- 6113390	28-02-91
		CA-A- 2023630	24-02-91
		JP-A- 3163015	15-07-91

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